

Complete Summary

GUIDELINE TITLE

The use of prophylactic anticonvulsants in patients with brain tumours: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Perry J, Zinman L, Laperriere N, Chambers A, Lloyd N, Spithoff K, Neuro-oncology Disease Site Group. The use of prophylactic anticonvulsants in patients with brain tumours: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Oct 11. 23 p. (Evidence-based series; no. 9-4). [16 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Brain tumors

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Neurological Surgery
Neurology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate whether patients with newly diagnosed brain tumours should receive prophylactic anticonvulsants to reduce seizure risk
- To evaluate the best practice for patients with brain tumours who are taking anticonvulsant medications but who have never had a seizure

TARGET POPULATION

Adult patients with newly diagnosed brain tumours in the peri- and postoperative period and beyond

This document will focus upon patients with brain tumours who have never had a seizure.

INTERVENTIONS AND PRACTICES CONSIDERED

Prophylactic anticonvulsants:*

1. Phenytoin
2. Divalproex sodium
3. Phenobarbital

*Routine use is not recommended (see "Major Recommendations" for context).

MAJOR OUTCOMES CONSIDERED

- Incidence of seizures
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (1966 to June 2005) and the Cochrane Library (2005 Issue 2) databases were searched using "anticonvulsant" (Medical subject heading (MeSH) or "antiepileptic drugs" (MeSH) combined with the keywords "glioma", "glioblastoma" and "brain tumours". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The Canadian Medical Association (CMA) Infobase (<http://www.cma.ca/cpgs/index.asp>), the National Guideline Clearinghouse (<http://www.guideline.gov/index.asp>), and other Web sites were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Inclusion Criteria

Fully published articles or abstracts were selected for inclusion in this systematic review if they:

1. Reported results of randomized controlled trials (RCTs) or meta-analyses of RCTs comparing patients with brain tumours treated with prophylactic anticonvulsants with patients with brain tumours not treated with prophylactic anticonvulsants or comparing various anticonvulsant-tapering strategies in patients with brain tumours. Sufficient follow-up time was required.
2. Included patients without a history of seizures.
3. Reported data on the incidence of seizures for each intervention group or adverse effects.
4. Clinical practice guidelines from other guideline development groups evaluating the use of prophylactic anticonvulsants in brain tumour patients were also eligible for inclusion.

Study Exclusion Criteria

1. Due to resource limitations, publications in languages other than English were excluded.
2. Letters and editorials were excluded.

NUMBER OF SOURCE DOCUMENTS

One evidence-based practice guideline, five randomized controlled trials, one systematic review, and one retrospective review were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

To estimate the overall effect of prophylactic anticonvulsants in patients treated with or without anticonvulsants, the incidence of seizures (the number of patients who suffered from at least one seizure by the end of the study and the number of patients included in the analysis by the investigators) were abstracted from the published reports of individual randomized controlled trials (RCTs). The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: May 2004; © 2004 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration. Combining data in this manner assumes a constant hazard ratio of risks for the groups being compared. Results are expressed as relative risks (RR) (also known as risk ratios) with 95% confidence intervals (CI), where an RR for the incidence of seizures less than one indicates fewer seizures in the experimental group. Conversely, an RR greater than one suggests that patients in the control group experienced fewer seizures. The RR is calculated by taking the ratio of the proportion of patients who have had a seizure in the experimental treatment group to the proportion of patients who have had a seizure in the control group. The random-effects model was used for pooling across studies in preference to the fixed-effects model, as the more conservative estimate of effect.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Only five randomized controlled trials (RCTs) have tested the effects of anticonvulsants for the primary prophylaxis of seizures in patients with newly diagnosed brain tumours. No studies have been disease-specific, and all included a mixture of both primary and secondary brain tumours. All were heterogeneous with respect to inclusion criteria and the anticonvulsants used in the study.

Anticonvulsants are problematic in brain tumour patients. The studies of Glantz et al and Forsyth et al. demonstrate that the rate and intensity of anticonvulsant-

related side effects may be higher in patients with brain tumours when compared to patients with seizure disorders from other causes. In addition, the anticonvulsants tested in those RCTs were in the class of enzyme-inducing anticonvulsants and are expected to have pharmacodynamic interactions with other medications commonly used in the treatment of those patients. In particular, interactions between enzyme-inducing anticonvulsants and chemotherapy are of significant concern. No studies have tested the newer generation of anticonvulsants that, in general, are characterized by fewer adverse effects and minimal drug interactions.

Because those clinical trials were all small, it is not possible to determine if there are special subgroups of patients at increased risk of seizures. Intuitively, patients with tumours near the motor strip, with cortically based tumours, or hemorrhagic tumours may be at increased risk of seizures; however there are no data to support this assumption. Clinicians must therefore individualize treatment for those patients. Tumour-related factors such as location must be integrated with patient preferences and quality of life (QOL), in addition to concomitant medications, in order to reach treatment decisions.

From the larger RCTs and the meta-analysis, it is clear that conventional anticonvulsants (phenytoin, valproic acid, and phenobarbital) confer at best a 25% reduction in the risk of seizures, with the incremental risk of adverse effects and drug interactions. The Neurology Disease Site Group (DSG) felt that the statistical power of those trials reliably excluded a clinically important reduction in seizure risk for seizure-naïve patients with newly diagnosed primary and secondary brain tumours. Thus, the routine use of postoperative anticonvulsants is not recommended in those patients, especially in light of a significant risk of serious adverse effects and problematic drug interactions. This recommendation is in agreement with the American Academy of Neurology (AAN) practice parameter.

The newer anti-epileptic medications may overcome some of these issues but have not been tested in clinical trials. No recommendations can be made regarding the use of those medications; however, a randomized controlled clinical trial, informed by the analysis and the suggestions by Forsyth et al., should be considered.

In the survey of Ontario practitioners, 74% of respondents indicated that they did not recommend the routine use of anticonvulsants in seizure-naïve patients with newly diagnosed brain tumours. Thus, the current practice is consistent with the recommendation of this guideline. The pre-guideline survey is presented in Appendix 1 in the original guideline document, and the results of the two case scenarios are shown in Table 3 in the original guideline document. Respondents were asked to indicate which response most closely matched their usual practice.

For patients who are already on anticonvulsants but have never had a seizure, there is very little evidence to guide treatment. The AAN practice parameter recommends considering a taper and discontinuation of anticonvulsants; however, only one small retrospective clinical trial has attempted to address that issue. There is insufficient evidence to recommend for or against the tapering of anticonvulsants in this situation, and, therefore, treatment must be individualized. In the Ontario practice survey, essentially equal numbers of practitioners would maintain anticonvulsants, withdraw them, or have a discussion and allow a

patient-based decision. Thus, current practice appears to reflect the lack of data that addresses this very specific question.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Neuro-oncology Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC).

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following review and discussion of Sections 1 and 2 of the original guideline document and review and approval of the report by the PEBC Report Approval Panel, the Neuro-oncology DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Methods

Feedback was obtained through an electronic survey of 55 practitioners in Ontario (medical oncologists, radiation oncologists, neurologists and neurosurgeons). The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was emailed on June 22, 2006. Follow-up reminders were sent on July 21 and August 4, 2006. The Neuro-oncology DSG reviewed the results of the survey.

This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Neuro-oncology DSG.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The routine use of postoperative anticonvulsants is not recommended in seizure-naïve patients with newly diagnosed primary or secondary brain tumours, especially in light of a significant risk of serious adverse effects and problematic drug interactions. This recommendation is in agreement with the American Academy of Neurology (AAN) practice parameter.
- There is insufficient evidence to support or refute the use of anticonvulsants in the perioperative period for patients with brain tumours who have never had a seizure.
- There is very little evidence to guide treatment for patients who are already on anticonvulsants but have never had a seizure. There is insufficient evidence to recommend whether or not anticonvulsants should be tapered in this situation and therefore treatment must be individualized.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by one evidence-based practice guideline, five randomized controlled trials, one systematic review, and one retrospective review.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Results of four randomized controlled trials (RCTs) that compared anticonvulsants to placebo or no treatment in patients with brain tumours and no history of seizures suggested no benefit for the long-term use of prophylactic anticonvulsants. The trials were small and insufficiently powered.
- Pooled results of 518 brain tumour patients from five RCTs demonstrated no benefit for anticonvulsants (relative risk [RR] 1.04, 95% confidence interval [CI] 0.70-1.54, $p=0.84$), reliably ruling out a clinically significant reduction in the incidence of seizures for patients who received anticonvulsants compared to no anticonvulsants.
- A published meta-analysis of RCTs including patients with no history of seizures indicated no benefit for prophylactic anticonvulsant treatment for early-onset seizures within one week of treatment initiation (odds ratio [OR] 0.91; 95% CI, 0.45-1.83, $p>0.05$). Analysis of long-term efficacy also

showed no benefit for prophylactic anticonvulsants (OR 1.01; 95% CI, 0.51-1.98, $p>0.05$).

POTENTIAL HARMS

Anticonvulsant use in patients with brain tumours is associated with potential adverse effects and drug interactions, particularly when used in combination with radiotherapy or chemotherapy. Adverse effects reported in clinical trials include rash, nausea, and hypotension. Clinicians should be aware of emerging evidence for the interaction between enzyme-inducing anticonvulsants and newer systemic chemotherapy agents in the experimental setting.

QUALIFYING STATEMENTS

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- Although there is insufficient evidence to support or refute the use of perioperative anticonvulsants in patients with brain tumours, there is evidence to suggest a role for perioperative anticonvulsants in general patient populations undergoing craniotomy to prevent early seizures.
- The anticonvulsants tested in randomized controlled trials (RCTs) are in the class of enzyme-inducing anticonvulsants, including phenytoin, phenobarbital, and divalproex sodium. No RCTs have been published that examine the efficacy of the newer generation of anticonvulsants for the prevention of seizures in patients with brain tumours.
- Anticonvulsant use in patients with brain tumours is associated with potential adverse effects and drug interactions, particularly when used in combination with radiotherapy or chemotherapy. Adverse effects reported in clinical trials include rash, nausea, and hypotension. Clinicians should be aware of emerging evidence for the interaction between enzyme-inducing anticonvulsants and newer systemic chemotherapy agents in the experimental setting.
- Patients with tumours near the motor strip, cortically based tumours, or hemorrhagic tumours may be at increased risk of seizure; however, there are no data to support this assumption. The RCTs included in this review were small and heterogeneous with respect to patient inclusion; therefore, it was impossible to determine whether subgroups of patients might benefit from prophylactic anticonvulsants.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Oct

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Neuro-oncology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Neuro-oncology Disease Site Group (DSG) were asked to disclose potential conflicts of interest relating to the topic of this systematic review and meta-analysis. No conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 28, 2008.

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